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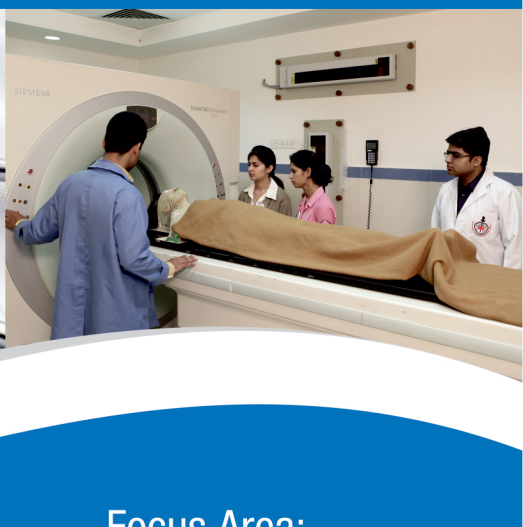

Focus Area:

GALLBLADDER CANCER

Rajiv Gandhi Cancer Institute and Research Centre

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From the Desk of Director Research

Gallbladder cancer (GBC) is an uncommon disease in majority of the countries despite being the most common and aggressive malignancy of biliary tree. Globally, about 1,78,101 cases of GBC are estimated to have occured in the year 2015. New cases and deaths from gallbladder and other biliary cancers in the United States in 2015 were approximately 10,910 and 3,700 respectively. In India, this malignancy is more prevalent in north and north-eastern regions of the country while southern India has low incidence rate in both the sexes. It is the commonest digestive cancer in north Indian women.

The most common symptoms caused by GBC are jaundice, pain and fever. Risk factors for the malignancy can be divided into four broad categories, including patient demographics, gallbladder abnormalities, patient exposures and infections. The disease is difficult to detect and diagnose as there are no signs or symptoms in the early stages. GBC typically presents in one of three ways that is, malignancy suspected preoperatively, malignancy discovered accidentally at cholecystectomy performed for presumed benign disease, and malignancy diagnosed incidentally at pathological examination following routine cholecystectomy. Over two-thirds of patients with GBC are only diagnosed during surgery or postoperatively. Adenocarcinoma is the most common histologic type, accounting for 98% of all gallbladder tumors. As such, this remains a highly lethal disease, with only 10% of all patients presenting at a stage amenable to surgical resection. Even among those suitable for resection, the anatomical complexity of the portobiliary hepatic system, the morbidity/mortality associated with liver resection and the risks of tumoral spread indicate a high mortality rate. Additionally, among patients that do undergo surgical resection, the recurrence rates remain high.

Chemotherapy is used in the adjuvant and palliative treatment of GBC. Because of the rarity of this disease, the benefit of adjuvant treatment remains unverified and no standard adjuvant treatment protocol has been defined. While GBC's tendency for locoregional spread and recurrence suggests that it is a rational target for intraoperative and postoperative radiotherapy, the role of adjuvant radiotherapy is poorly described in the literature with conflicting and largely disappointing results. At present, targeted therapy has limited role in the management of this malignancy. Historically, GBC had an overall 5-year survival less than 5%. Therefore, the future for improved success in the management of this disease should be aimed at the development of sensitive and specific screening strategies with improved molecular understanding of the pathogenesis of this "orphan disease."

The present issue of the Cancer News highlights the newer advances in the field of "Gallbladder Cancer" and features the regular articles, such as Special Feature, Guest Article, Perspective and In Focus. We are grateful to Dr B R Shrivastav, Director, Cancer Hospital and Research Institute, Gwalior for the "Guest Article"; Dr Rakesh Kapoor, Prof Dept of Radiotherapy, PGIMER, Chandigarh for the "In Focus".

Suggestions / comments from the readers are welcome. Wishing our readers a Happy, Prosperous and Healthy New Year 2016!

Dr D C Doval

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SPECIAL FEATURE

SYSTEMIC TREATMENT OF GALLBLADDER CANCER

Gallbladder cancer (GBC) represents the most common and aggressive type among the biliary tree cancers (BTCs). Complete surgical resection offers the only chance for cure; however, only 10% of patients with GBC present with early-stage disease and are considered surgical candidates. Among the patients who do undergo "curative" resection, recurrence rates are high. Patients with unresectable or metastatic GBC have a poor prognosis.

Systemic therapy is used in curative and palliative setting in the management of gallbladder cancer in 3 situations: (1) in adjuvant therapy alone or in combination with radiation following surgical resection; (2) in locally advanced nonmetastatic unresectable disease alone or in combination with radiation therapy; and (3) in advanced metastatic disease.

There is a paucity of randomized controlled studies in the management of gallbladder cancer in relationship with systemic therapy due to the rarity of gallbladder and other biliary tract cancers. Most studies are inclusive of all biliary tract cancers and only a few gallbladder cancer-specific.

Resectable Gallbladder Cancer: Adjuvant Therapy

Evidence regarding adjuvant therapy in gallbladder cancer, with few exceptions, is mostly limited to retrospective studies. Most studies concerned small, heterogeneous groups of patients seen at a single institution. Several retrospective series and small phase II studies suggest better survival in patients who receive postoperative adjuvant treatment. The only phase III randomized trial regarding benefit of adjuvant therapy in gallbladder and biliary tract cancer is reported by the Japanese group. In this phase III multicenter trial, 508 patients with resected pancreaticobiliary cancer were randomly assigned two cycles of intravenous mitomycin and 5-FU (MF) followed by maintenance oral 5-FU until disease recurrence versus observation. In a subgroup of 140 patients with gallbladder cancer, 5-year disease-free survival (DFS) rates of patients treated with adjuvant MF was 20.3% compared with 11.6% with observation (P=0.02). The 5-year survival rate was significantly better in the adjuvant therapy group (26.0%) compared with the control group (14.4%) (P = 0.03)[1].

A meta-analysis which included 20 studies involving 6712 patients assessed the impact of chemotherapy, radiation therapy, or both the therapies as an adjuvant to curative-intent surgery for the management of biliary tract cancers comprising extrahepatic and gallbladder cancers. Of 6712 patients, 4915 were treated with surgery alone, and 1797 received adjuvant therapy. The meta-analysis reported a nonsignificant improvement in overall survival with any adjuvant therapy compared with surgery alone [odds ratio (OR), 0.74; P=0.06]. The association was significant when the two registry analyses were excluded. A nonsignificant benefit was also observed when disease sites were analyzed independently (gallbladder: OR, 0.81; 95% CI, 0.49 to 1.35; P=0.041). The benefit of adjuvant therapy was dependent on treatment modality. Patients who received chemotherapy (OR, 0.39; 95% CI, 0.23 to 0.66; P<0.001) or chemoradiotherapy (OR, 0.61; 95% CI, 0.38 to 0.99; P=0.049) derived greater benefit than patients who were treated with radiation therapy alone (OR, 0.98; 95% CI, 0.67 to 1.43; P=0.90). Nine studies reported nodal or margin positivity. Pooled data revealed a significant benefit for adjuvant chemotherapy or chemoradiation treatment (n=230) in node-positive disease (OR, 0.49; 95% CI, 0.30–0.80; P=0.004) or in cancers with R1 disease (OR, 0.36; 95% CI, 0.19 to 0.68; P=0.002)[2]. An exploratory analysis that demonstrated greater magnitude of benefit from adjuvant therapy in studies included patients with node-positive disease, R1 disease, or both diseases compared to studies that did not include patients with node-positive or R1 disease. Similar findings were also seen in Surveillance, Epidemiology, and End Results (SEER) based study that was not included in this meta-analysis. This study demonstrated that, with the exception of T1N0 patients, 6 months of chemotherapy or radiation after surgery was associated with a better survival.

Even though the meta-analysis favors adjuvant therapy in patients with high risk, that is, node-positive gallbladder cancer, it does not resolve the question of the benefit of adjuvant therapy in patients with low risk disease. Moreover, the best treatment strategy, for instance, chemoradiotherapy versus chemotherapy alone, in adjuvant setting is not known.

Locally Advanced Unresectable Gallbladder Cancer

The optimal management of patients with locally advanced and unresectable gallbladder cancer is controversial, and there is no internationally embraced standard approach. The options for patients with locally

advanced gallbladder cancers include fluoropyrimidine chemoradiation or gemcitabine-based chemotherapy (such as gemcitabine/cisplatin combination) or fluoropyrimidine-based chemotherapy. The available data suggest that tumor control is rarely achieved with external beam radiation alone. Most patients with locally advanced unresectable disease are treated with combination of chemotherapy and radiation rather than radiation alone. However, it is not known if chemoradiation therapy is superior to chemotherapy alone in this.

Metastatic Gallbladder Cancer

Systemic chemotherapy has shown significant but modest survival benefit in the management of advanced gallbladder cancer. A randomized trial compared systemic chemotherapy of gemcitabine plus oxaliplatin or 5-FU plus leucovorin versus best supportive care alone in 81 patients with unresectable gallbladder cancer[3]. Median overall survival in best supportive care and 5-FU/leucovorin groups was 4.5 and 4.6 months, respectively, versus 9.5 months in gemcitabine plus oxaliplatin group.

A pooled analysis of 104 chemotherapy trials involving 1,368 patients with biliary tract and gallbladder cancers that were conducted during 1985-2006 suggested differences in clinical behavior and responsiveness to chemotherapy between gallbladder and other biliary tract cancers. Pooled response rates and tumor control rates were 22.6 and 57.3%, respectively. Subgroup analysis showed superior response rate for gallbladder cancer compared with cholangiocarcinoma (36 versus 18%) but shorter overall survival for gallbladder cancer (7.2 versus 9.3 months)[4].

Fluoropyrimidine-Based Regimens: 5-FU and 5-FU-based regimens were among the first reported in gallbladder cancers. In old trials, 5-FU alone or 5-FU-based combination therapies demonstrated objective response rates from 0 to 34% and median survival of four to six months in patients with advanced gallbladder and biliary tract cancers. In contrast, most recent studies using infusional 5-FU combination therapy reported higher response rates and better overall survival. In one study, infusional 5-FU in combination with cisplatin resulted in partial response in six patients (24%). Median survival for patients with gallbladder cancer was 11.5 months[5].

Capecitabine is an orally active fluoropyrimidine derivative that has demonstrated efficacy in gallbladder cancer both as a single agent and in combination with cisplatin, gemcitabine, and oxaliplatin. For instance, in a study involving 63 patients with hepatobiliary malignancies, which included eight patients with gallbladder cancer, capecitabine produced an objective response in four patients with gallbladder cancer, two of which produced complete response[6]. In another trial involving 65 patients with biliary tract tumors, capecitabine was used in combination with oxaliplatin. Of 65 patients, 27 had gallbladder cancer. The patients with gallbladder cancer had a total disease control rate of 63% (one complete response, seven partial responses, and nine patients with stable disease) and a median survival of 8.2 months.[7]

Gemcitabine-Based Regimens: Gemcitabine is an active agent both as monotherapy and in combination regimens. It has been extensively evaluated in patients with metastatic gallbladder and biliary tract cancers. The clinical benefit rates (partial response plus stable disease) with single agent gemcitabine varied from 15 to 60% with overall response rates being as low as 7%. Most studies reported median survival of 10 months or less. In contrast, reported response rates with gemcitabine combination therapies varied from 17% to 50%, with median overall survival of up to 14 months. At least four studies of gemcitabine plus cisplatin in patients with advanced gallbladder and biliary tract cancers have been reported. The reported response rates ranged from 21% to 34.5% and median survival times varied from 9.3 to 11 months. The substitution of carboplatin for cisplatin decreases the severity of nonhematologic toxicity, such as nausea, vomiting, nephropathy, and neuropathy; however, myelosuppression is sometimes worse. In a small trial, combination of gemcitabine and carboplatin produced response rate of 37% and median overall survival of about 11 months. Several trials have demonstrated efficacy and good tolerability with a combination of gemcitabine and oxaliplatin. The Groupe Coopérateur Multidisciplinaire en Oncologie study evaluated 56 patients with gallbladder and biliary tract cancers[8]. These patients were treated with gemcitabine-oxaliplatin combination and were stratified based on Eastern Cooperative Oncology Group performance status score (0–2 versus >2) and bilirubin. The median overall survival of patients with good performance status was almost double that of patients with poor performance status (15.4 months versus 7.6 months). Of note, was that even patients with poor performance status tolerated this regimen fairly well. Others report a far lower objective response rate with this regimen in advanced gallbladder cancer (1 of 23 patients, 4%) as compared to nongallbladder biliary tract carcinomas (9 of 44, 21%). Similar to gemcitabine and platinum compounds combination, gemcitabine and the oral 5-FU prodrug capecitabine combination has been associated with higher

response rates than gemcitabine plus 5-FU for advanced biliary and gallbladder tumors. At least four phase II trials reported response rates up to 32% and a median survival of approximately 13 to 14 months.

The result of a randomized phase III trial that reported improvement in outcomes of patients with locally advanced or metastatic biliary tract and gallbladder cancers, who were treated with combination therapy was a major breakthrough in management of advanced gallbladder and biliary tract cancers[9]. In this trial, 410 patients with locally advanced (25%) or metastatic bile duct (n=242), gallbladder, (n=149) or ampullary (n=20) cancer were randomly assigned to eight courses of cisplatin (25 mg/m^2) followed by gemcitabine (1000 mg/m^2) on days 1 and 8, every 21 days, or gemcitabine alone (1000 mg/m^2 on days 1, 8, and 15, every 28 days). At a median follow-up of 8.2 months, median progression-free survival (8 versus 5 months) and median overall survival (11.7 versus 8.1 months) were better with combination therapy.

Taxanes and Other Chemotherapeutic Agents: Other chemotherapeutic agents have demonstrated limited benefit in gallbladder and biliary tract cancers. For instance, when paclitaxel was given every 21 days it demonstrated minimal efficacy in gallbladder cancer. Likewise, the addition of pemetrexed to fixed-dose-rate gemcitabine, in a biweekly schedule, did not enhance the activity of gemcitabine in patients with biliary tract or gallbladder carcinoma. Whereas docetaxel has shown a response rate of 20% in patients with advanced gallbladder and biliary tract cancers, single agent irinotecan demonstrated partial response rate of 8% and clinical benefit rate (partial response and stable disease) in 48%. Based on the trial by Valle et al[9] for patients with metastatic gallbladder cancer and good performance status, combination of cisplatin and gemcitabine is standard first-line systemic therapy. In patients with borderline performance status, single agent gemcitabine or capecitabine is a reasonable alternative option.

Second-Line Therapy in Gallbladder Cancer: Currently there is no "standard" second-line therapy after failure of first-line gemcitabine and cisplatin therapy in patients with gallbladder cancer. In a preliminary report covering 18 patients with advanced gemcitabine-refractory pancreaticobiliary cancer who received CAPOX, one had a partial response, and 8 patients had stable disease with the median progression-free survival of about 16 weeks in all patients[10]. In patients with good performance status oxaliplatin-based regimen, 5-FU/capecitabine, taxanes, or irinotecan-based therapy may be considered following progression on cisplatin/gemcitabine.

Targeted Therapies in Gallbladder Cancer: Common mutations reported in gallbladder cancer are KRAS (10%–67%), EGFR (63%), BRAF (0% to 33%), and erbB2/HER2 (16%–64%)[11]. Early data suggest possible benefit from blockade of the epidermal growth factor receptor by the oral tyrosine kinase inhibitor erlotinib or anti-EGFR monoclonal antibody cetuximab. A randomized phase II study comparing gemcitabine plus oxaliplatin alone with the same chemotherapy regimen in combination with cetuximab demonstrated a higher 4-month PFS rate with the addition of cetuximab (44% versus 61%, resp.)[12].

Vascular endothelial growth factor (VEGF) is overexpressed in biliary tract cancers and has been proposed as a therapeutic target. The efficacy of bevacizumab, a monoclonal antibody targeting VEGF, in combination with erlotinib was assessed in a phase II trial. Nine patients had partial response to double targeted therapy that was sustained beyond four weeks in six patients, with median response duration of 8.4 months. Overall stable disease was observed in about half of the treated patients. Sunitinib and sorafenib have shown modest benefit in biliary tract and gallbladder cancers. Likewise, selumetinib a BRAF inhibitor, triapine a ribonucleotide reductase inhibitor, and imatinib a tyrosine kinase inhibitor, have shown some efficacy in gallbladder and biliary tract cancers. In contrast, lapatinib targeting erB2/HER2 and bortezomib, a proteasome inhibitor, failed to demonstrate benefit in gallbladder and biliary tract cancers.

Conclusions

Gallbladder cancer is uncommon with a high case fatality occurring over a wide geographical distribution. Most gallbladder cancers, unfortunately, are discovered incidentally at routine cholecystectomy or present as advanced stage disease. At diagnosis, less than ~20% of patients are candidates for curative surgery. The future, therefore, for improved success in the management of this disease may have to be directed towards the development of sensitive and specific screening strategies with relevant improved molecular understanding of the underlying pathogenesis of this "orphan disease."

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PERSPECTIVE

PET/CT AND ITS APPLICATIONS IN INCIDENTAL GALLBLADDER CANCER

Gallbladder carcinoma is a relatively uncommon but quite aggressive malignancy arising from the gallbladder and the cystic duct. Anatomic factors are responsible for early local invasion and thus the tumor invades the liver and biliary tree easily contributing to its poor outcome and high mortality. It also has a propensity for invasion to lymph nodes, hematogenous spread and implanting on peritoneal surfaces. Diagnosis of carcinoma gallbladder is usually late as it exhibits non-specific symptoms and signs mostly mimicking other non- malignant conditions like cholelithiasis or chronic cholecystitis and quite frequently co-exists with these conditions. It carries a poor prognosis with a reported 5-years survival of 5-10% in most large series. Majority of cases are detected incidentally at surgical exploration for benign gallbladder disease.

Fewer than 5000 are diagnosed each year in the United States with the incidence rate of 1 to 2 per 100,000. However, there is again a prominent geographic variability in the incidence that correlates well with the prevalence of cholelithiasis. Relatively high rates are seen in South American and North Asian countries. This is mainly because all these populations share a high prevalence of gallstones and/ or salmonella typhi infection both of which are recognized risk factors. The risk also seems higher in those with larger gallstones and patients with stones larger than three cm have a ten-fold higher risk of carcinoma gallbladder compared to those with stones which are less than 1 cm. Other risk factors include increasing age, female gender (women are affected two to six times more often than men), chronic cholecystitis, porcelain gallbladder, gallbladder polyps, primary sclerosing cholangitis and congenital anomaly of pancreaticobiliary duct junction. Lifestyle factors, such as obesity, diabetes and smoking are also contributory. Dysplasia and metaplasia of the epithelial lining of the gallbladder is a causative factor. Gastric metaplasia is the most common metaplasia in gallbladders and intestinal metaplasia occurs with increasing age and in association with gallstone disease. Squamous metaplasia tends to be associated with gallstones and can lead to squamous dysplasia or squamous cell carcinoma. Adenomas occur in 0.3% -0.5% of the population. The risk of malignant transformation increases with the size of the adenoma and the amount of papillary pattern. Approximately 98% of gallbladder cancers are of epithelial origin, with more than 90% identified as adenocarcinomas. Adenocarcinomas may be well, moderately, or poorly differentiated depending on the degree of gland formation. The remaining subtypes include adeno-squamous or squamous cell carcinoma, small cell neuroendocrine tumors, sarcoma, and lymphomas. Most of these tumors originate in the gallbladder fundus (60%) with the remainder in the body (30%) and neck. Rare non-epithelial tumors include sarcomas, lymphomas, carcinoid tumors, and metastases.

Clinical diagnosis of gallbladder carcinoma is challenging due to lack of specific signs and symptoms and therefore diagnosis is made quite late into the disease or as an incidental finding after cholecystectomy done for cholecystitis or other reasons. Most of the patients present with right upper quadrant abdominal pain. Weight loss, anorexia, nausea and vomiting are commonly

associated. Elevated serum carcinoembryonic antigen (CEA) levels may be helpful. Imaging studies may reveal a mass replacing the normal gallbladder, diffuse or focal thickening of the gallbladder wall, polypoidal mass within the gallbladder lumen or as a gallbladder fossa mass. Mass replacing the gallbladder fossa is the most common presentation. Adjacent organ invasion, primarily involving the liver and biliary obstruction is often present at diagnosis. Periportal and peripancreatic lymph nodes, hematogenous and peritoneal metastases may also be seen.

Ultrasonography is most often the first imaging modality to investigate gallbladder disease due to its relatively low cost and ease of availability. However, in the case of carcinoma gallbladder, its use is limited in early diagnosis and staging. This limitation can be overcome by combining endoscopy with ultrasound (EUS) and in recent years endoscopic ultrasound has gained increasing popularity in assessing of gallbladder carcinoma. This technique enables assessment of the depth of tumor invasion into the wall of the gallbladder and presence of lymphadenopathy at the porta hepatis and peripancreatic regions. Conventional US appears to be quite reliable in the detection of masses and the extent of hepatic invasion, but it is limited in its ability to detect lymphnode and peritoneal disease.

Computed Tomography (CT) is a better modality for evaluation of thickness of the portions of the gallbladder wall that are obscured on ultrasound. Diffuse symmetric wall thickening is more likely to suggest a non-neoplastic process. Carcinoma gallbladder is usually hypodense on unenhanced CT with up to 40% showing hypervascular foci of enhancement equal or greater than that of the adjacent hepatic parenchyma. Lymphatic spread usually occurs through the hepatoduodenal ligament to nodal stations near the pancreatic head. The sensitivity of contrast enhanced CT in detecting gallbladder neoplasms has been reported to be as high as 90% and is particularly effective in assessing resectability of gallbladder tumors providing valuable information on local and vascular invasion as well as hematogenous and lymph node metastases. MRI is more useful in differentiating benign from malignant disease. MR angiography and MRCP can be added to facilitate the diagnosis of vascular and biliary infiltration that is essential before attempting curative resection. Any focal or eccentric stenosis, irregularity of the lumen or abrupt amputation is suggestive of invasion.

An intense accumulation of 18 F-FDG in the region of the gallbladder suggests malignancy although it lacks specificity in differentiating primary gallbladder carcinoma from other regional malignant lesions, such as HCC, cholangiocarcinoma or metastatic disease. PET, however has a promising role in the detection of unsuspected metastases that may modify staging and treatment protocols. Incidental carcinoma at histology after cholecystectomy for cholelithiasis can be seen in about 3 % of specimens, warranting routine histopathological examination. However, even with routine histopathological evaluation, some cases may be missed or remain occult. In many such instances, the diagnosis of malignancy is made only later after the appearance of metastasis. In both these scenarios histopathology after cholecystectomy is generally negative for malignancy. However, years later these patients can present with port site metastasis suggesting the earlier presence of occult gallbladder carcinoma. Port site recurrence of carcinoma gall bladder after laparoscopic cholecystectomy is not rare. Various factors have been proposed that could possibly be involved in the development of such port site metastases and port site resection has been attempted in patients with incidentally discovered disease after laparoscopic cholecystectomy. However, this preventive excision has not been found to affect outcome. 18F-FDG PET/CT is a robust tool in oncological imaging and has been used for staging, restaging and prognostication of this disease. Utility of 18F-FDG PET/CT for detection of port site metastasis with high sensitivity has been documented in many studies. In fact the major implications of 18F-FDG PET/CT can be determined in this clinical setting. PET/CT can, during follow-up can detect port site metastasis, demonstrate the disease extent and rule out any other sites of metastasis, if present. PET/CT can demonstrate additional abdominal nodal metastasis in normal sized lymph nodes. This finding can have a significant impact on further therapeutic management and prognosis. While patients with port site metastasis could be managed with surgical excision of the lesion, often supplemented with chemotherapy, those with widespread metastasis will require palliative chemotherapy. PET/CT can show or rule out any other primary tumor as the source of metastasis in a setting in which the initial histopathology is negative for primary in gallbladder.

In conclusion, 18F-FDG PET/CT can play an important role in the staging, restaging and response evaluation in patients of carcinoma gall bladder and has an additional role to play in patients presenting with late port site metastasis from occult gall bladder malignancy after laparoscopic cholecystectomy for cholelithiasis.

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GUEST ARTICLE

EPIDEMIOLOGICAL SCENARIO OF GALLBLADDER CANCER

Abstract

Gallbladder cancer (GBC) is one of the most common cancers of biliary tract. Worldwide incidence is still increasing year by year. Late diagnosis, poor prognosis and non-effective therapeutic options are the major reasons for increase in the number of deaths. Middle aged females are more affected than other age groups. Incidence of gallbladder varies in different geographical areas in India. Genetic and environmental factors are considered to be the most important causing factors of gallbladder cancer. Here, we have discussed the current global and national epidemiological trends of this cancer. We report a glimpse of incidence of gallbladder cancer in north central India in the last decade.

Introduction

Gallbladder cancer is an uncommon cancer; but a deadly disease. Various reports have suggested gallbladder cancer to be a female biased cancer and it affects the middle age patients. Since there is no any potential early diagnostic biomarker for gallbladder cancer, survival rate of patients is very low. More than 80% of the reports available so far have found the presence of gallstone in gallbladder cancer; but the pathogenic relationship between them remains to be elucidated. There are geographical variations of its incidence worldwide. Incidence is high in Asian countries and in few American countries, such as Chile, The available data indicates high incidence of GBC in north and eastern states of India (Sen et al, 2002; Barbhuiya et al, 2009; Barbhuiya et al, *in press*). The possible pathological conditions associated with increased risk of gallbladder carcinoma include cholecystoenteric fistula, porclain gallbladder, ulcerative colitis, adenomyomatosis (Kurihara et al, 1993; Ootani et al., 1992), polyposis coli (Bombi et al, 1984), Gardner's syndrome (Walsh et al, 1987), and anomalous connection between common bile duct and the pancreatic duct (Chijiwa and Koga 1993; Kinoshita et al., 1984; Morohoshi et al., 1990). Various molecular mechanisms are involved in the gallbladder carcinogenesis. Development of appropriate potential biomarker of GBC is of utmost importance (Tekcham et al., 2015). Besides genetics, recent investigations suggest the possible role of epigenetics in gallbladder cancer (Singh et al. 2015). Here we discuss the epidemiology of gallbladder cancer in global and Indian scenarios. Finally, a hospital based report of ten years covering the period of 2004-2013 is also briefly described.

Symptoms of Gallbladder Cancer

Like other diseases, gallbladder cancer also displays symptoms. Known symptoms include gallstone formation, jaundice, pain in the right lower abdomen, nausea and vomiting, anorexia, weight loss etc. We often experience the tumor or the stone or inflammation formed inside the gallbladder which obstructs the passage of bile to cystic duct. This causes consistent pain in the abdomen. Many cases of gallbladder cancer are detected at late

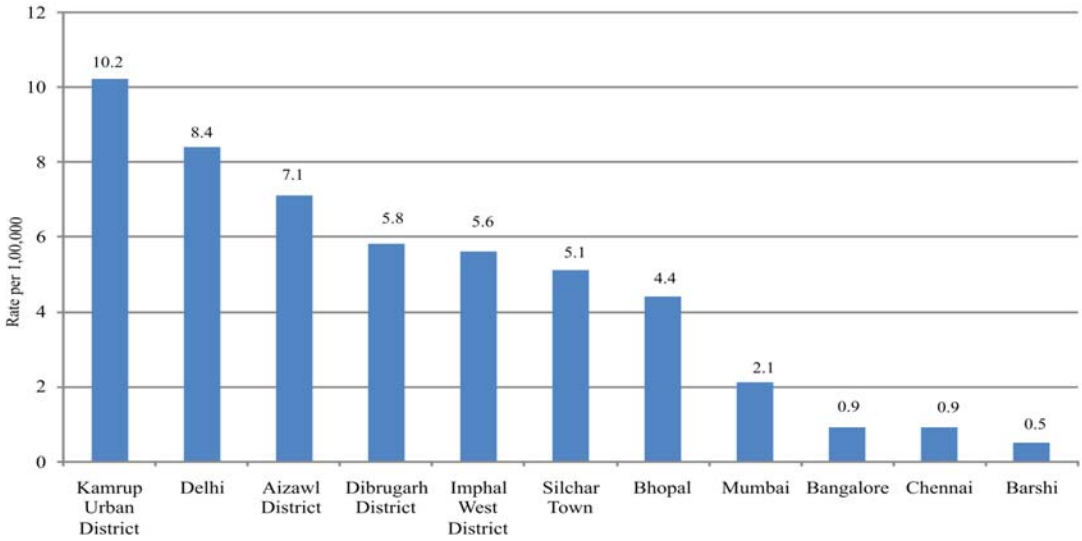

Figure 1: Comparison of Age Adjusted Incidence Rates of GBC(AAR's) (female) of North East PBCR's (2003-2004) with the AAR's of other PBCR's (2001-2003) (This graph is reproduced from the PhD thesis) (Singh et al, 2015).

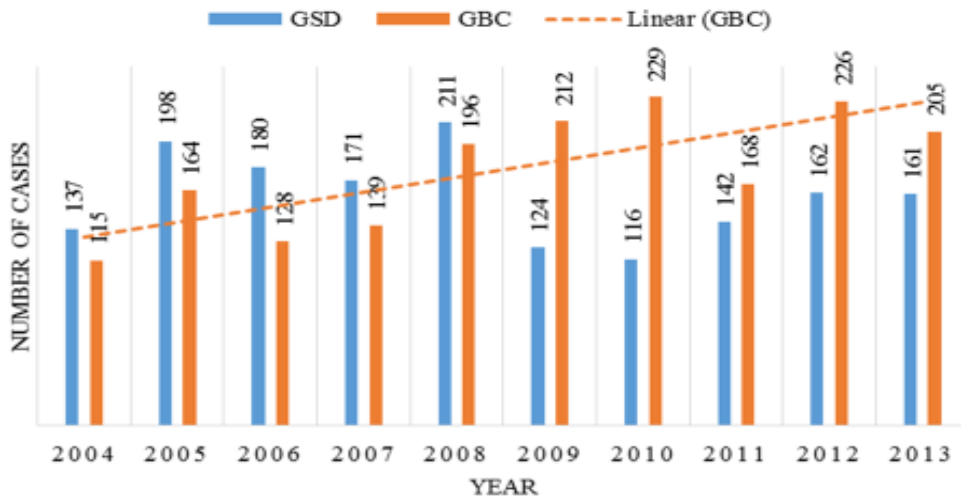

Figure 2: Histogram showing comparative number of GBC and GSD cases registered during 2004-2013. This shows an increasing trend of GBC cases in the last decade

advanced stage due to lack of efficient and potential marker to confirm the early diagnosis. Patients with bile duct cancer most often become symptomatic when the tumor mass obstructs (blocks) the path to drain bile. In fact, approximately 1% of patients who undergo cholecystectomy (surgical removal of the gallbladder) for suspected cholecystitis prove to have unsuspected gallbladder carcinoma. Distal bile duct tumors near the ampulla of Vater, the point at which the bile drains into the bowel, also obstruct the pancreatic duct leading to inflammation of the pancreas (pancreatitis).

Potential Risk Factors of Gallbladder Cancer

Risk factors for GBC, which might not be independent of each other, include genetic predisposition, geographic variation and ethnicity, increasing age, female gender, chronic inflammation, congenital developmental abnormalities, low socio-economic status, low frequency of cholecystectomy for gallbladder diseases and exposure to certain chemicals (Barbhuiya et al, 2009; Barbhuiya et al, *in press;* Piehler & Crichlow, 1978). Population based study carried out in China showed higher risk of GBC with higher parity, younger age of first birth, late age at menarche and presence of stones (Andreotti et al, 2010).

Epidemiology

Gallbladder cancer is one of the rarest and most lethal cancers having restricted survival rates on stage of diagnosis. Survival rate is closely related to the stage of the tumor, with 60% 5-year survival for stage 0 patients, 39% for stage I patients, 15% for stage II patients, 5% for stage III patients and 1% for stage IV patients (Donohue et al, 1998). The highest frequency of the

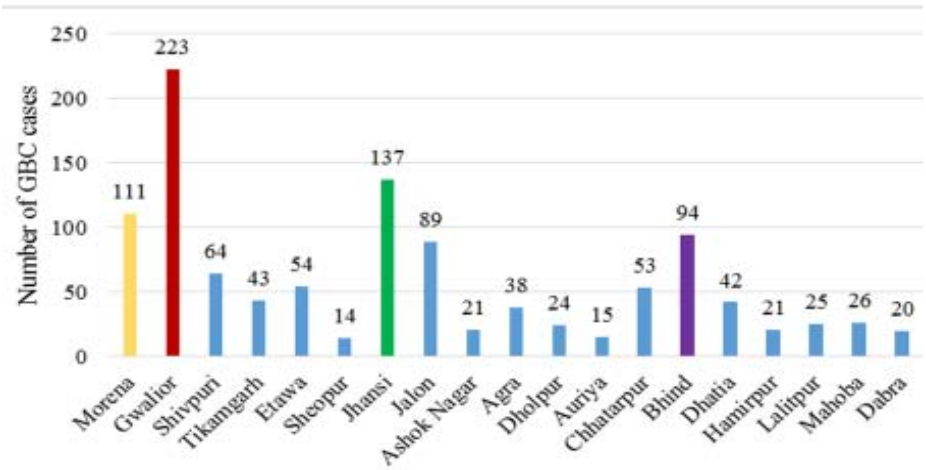

Figure 3: District-wise distribution of gallbladder cancer cases registered at CHRI, Gwalior, during 2004-2013 (10 years)

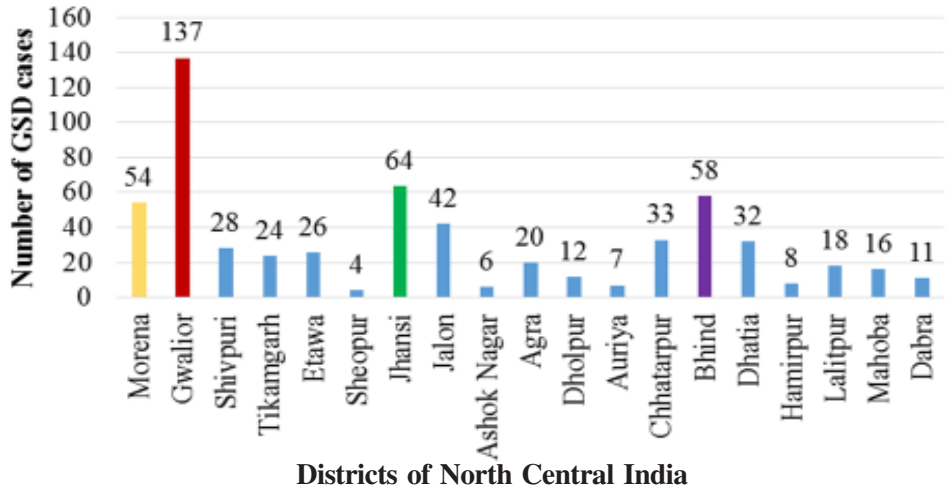

Figure 4: District-wise distribution of GSD cases registered at CHRI, Gwalior, during the last five years 2009-2013

cancer was found among females over the age of 65 (Tada et al, 1990). Gallbladder cancer is the 6th most common gastrointestinal malignancy in the United States, following cancers of the colon, pancreas, stomach, liver, and oesophagus (Greenlee et al, 2000). Its incidence is also high in north central India (Barbhuiya et al, 2009). Approximately one-fifth of patients with gallbladder carcinoma are with acute cholecystitis (Lam et al, 2005). Gallstones (Randi et al, 2006; Barbhuiya et al, 2009) and gallbladder inflammation (Piehler & Crichlow, 1978) have long been known to play a role in developing GBC. Gallstone diseases (GSD) and GBC are significantly associated; gallstones are present in more than 85% of patients with GBC (Barbhuiya et al, 2009; Barbhuiya et al, *in press;* Singh et al, 2012). The incidence of GBC is approximately 7 times more common in patients with gallstones and chronic cholecystitis than in those without gallstones (Nervi et al, 1988). Anomalous ancreatobiliary ductal junction (APBDJ) was reported to be an important risk factor for GBC (Kimura et al, 1985).

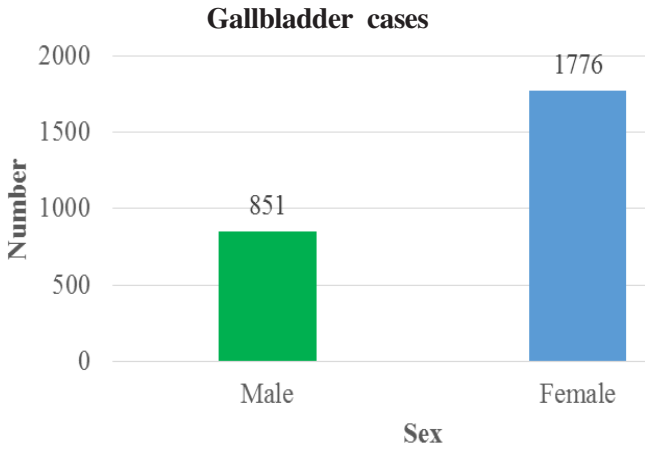

Figure 5: Histogram showing the number of male and female gallbladder cases (GBC+GSD) registered at CHRI, Gwalior during 2004-2013

Global Scenario: The highest incidence rate of gallbladder cancer is found among populations of the Andean area, North American Indians and Mexican Americans. Gallbladder cancer is up to three times higher among women than among men in all populations. In 2015, 4990 male and 5920 female new cases of gallbladder cancer are expected in USA. The number of deaths due to GBC are 1660 males and 2040 females (Siegel et al. 2015). The high incidence of GBC was reported from Delhi (21.5 per lakh) followed by South Karachi, Pakistan (13.8 per lakh) and Quito, Ecuador (12.9 per lakh) (Randi et al. 2008). The incidence of GBC is 7.8 per lakh in north central India (Barbhuiya et al. *in press*). The highest incidence rates in Europe are found in Poland, the Czech Republic, and Slovakia. Incidence rates in other regions of the world are relatively low. The highest mortality rates are also reported from South America, 3.5-15.5 per lakh among Chilean Mapuche Indians, Bolivians, and Chilean Hispanics. Intermediate rates, 3.7 to 9.1 per lakh, are reported from Peru, Ecuador, Colombia, and Brazil. Mortality rates are low in North America, with the exception of high rates among American Indians in New Mexico (11.3 per lakh) and among Mexican Americans (Lazcano-Ponce et al, 2001). The high mortality rate contrasts with the mean of the whole country, which had an age-adjusted mortality rate of 16.2 per lakh for women and 5.4 per lakh for men in 1991 (Chianale et al, 1990). There is a worldwide ethnic geographical distribution of incidence of GBC which correlates with the prevalence of cholelithiasis. The highest incidence rates of GBC (up to

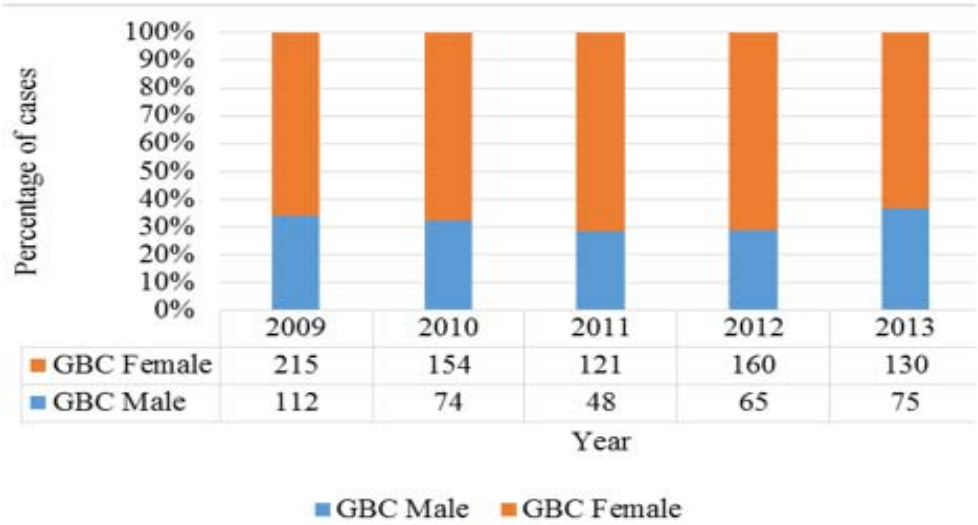

Figure 6: Comparison of number of GBC cases (female and male) during 2009-13

7.5 per lakh for men and 23 per lakh for women) are found among populations from western parts of the Andes, and in North American Indians, Mexican Americans, and inhabitants of northern India. Most of these populations have a high prevalence of gallstones and/or *Salmonella* infection (Parkin et al, 1997). In most of the European countries, age standardized mortality rates of GBC declined by 30% among women and by 10% among men in the 1990s, but, still the mortality rate was found high in central and eastern Europe (Levi et al, 2003). Between the early 1980s and mid-1990s, Biliary Tract Cancer (BTC) mortality rates fell in the United States and Australia. In contrast, Japan reported a rise of mortality rates for BTC (Khan et al, 2002). GBC was reported to be the first cause of death for cancer among women in Chile, and the mortality rate had not decreased since 1980s (Andia et al, 2006). Maram et al, (1979) and Nervi et al, (1998) reported 4-7 times increase of risk of GBC with gallstones. Frequency of GBC is 2-6 times more among women than among men, although the rate varies from one place to another in the world. In an epidemiological analysis carried out in Chilean population, the incidence rate of GBC varied from other populations. Most of GBC cases belonged to females (76.0%), urban residents (70.3%), Hispanic (83.7%), and illiterate class of less than 4 years of schooling (64.0%). GBC standardized incidence rate per 100,000 (SIR) of all cases were 17.5 (95%CI: 15.5–19.4), of females 24.3, and of males 8.6 ($p<0.00001$), of Mapuche 25.0 and of Hispanic 16.2 ($p=0.09$). The highest SIRs were in Mapuche (269.2) and Hispanic women (199.6) with less than 4 years of schooling. Lowest SIRs were among Hispanic men (19.8) and women (21.9) with greater than 8 years of schooling. Kaplan Meier Global 3-year survival analysis revealed 85% at stage I and 1.9% at stage IV, and median survival of 3.4 months. Independent poor prognostic factors were TNM IV, jaundice and non-incidental diagnoses (Bertran et al, 2010).

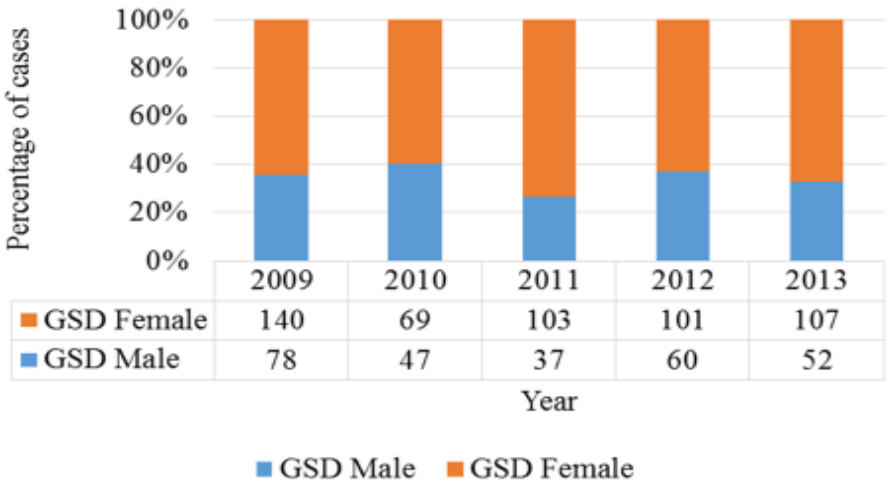

Figure 7: Comparison of numbers of GSD cases (female and male) during 2009-13

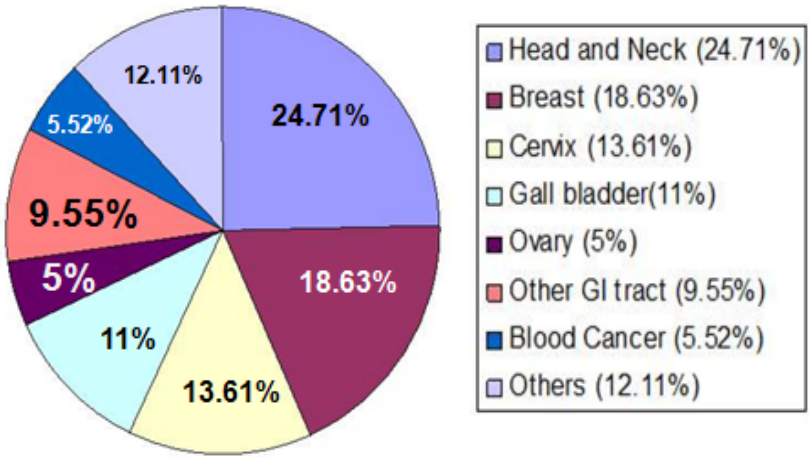

Figure 8: Pie diagram showing the distribution of cancers registered at CHRI. Gallbladder cancer is the 4th most common cancer (Source: CHRI data base)

Epidemiological survey conducted in Chinese population revealed various lipid molecules to be the major risk factor of biliary tract cancer. Individuals with a concentration of triglycerides to e"160 mg/dl, had a 1.4-fold risk of biliary stones (95% CI=1.1-1.9), 1.9-fold risk of gallbladder cancer (95% CI=1.3-2.8), and 4.8-fold risk of bile duct cancer (95% CI=2.8-8.1), as compared to the normal control group (normal range: 90-124 mg/dl). Subjects with low level of high-density lipoprotein (HDL) (<30 mg/dl) had 4.2-fold risk of biliary stones (95% CI 5 3.0-6.0), 11.6-fold risk of gallbladder cancer (95% CI=7.3-18.5), and 16.8-fold risk of bile duct cancer (95% CI=9.1-30.9), as compared to the control group (normal range: 40-49 mg/dl) (Andreotti et al, 2008).

National Scenario: Based on the reports of 50 years of cancer control in India, incidence of gallbladder cancer is found very high in three cities such as, Delhi, Bhopal and Mumbai (Website: www.mohfw.gov.in). GBC has an association with bile composition, food habit and gallstone formation (Shukla et al, 1993). Based on different population based cancer registries, GBC was found to be one of the most common causes of cancer related mortality in women in northern and north-eastern states of India (Nandakumar et al, 2005). A population based cancer registry, Kolkata, 1998-99, diagnosed 6,093 male and 5,607 female cancer patients (Sen et al, 2002). The published data of National Cancer Registry Program, Indian Council of Medical Research, reported the number of cases diagnosed from 2001-2003 per site as 494 males and 879 females in Delhi, 55 males and 61 females in Bangalore, 43 males and 64 females in Bhopal, 72 males and 58 females in Chennai, 235 males and 280 females in Mumbai and 6 males and 3 females in Barshi. A case study identifying risk factors of GBC was also reported in Delhi (Tyagi et al., 2008). Among GITC patients, high frequency of blood group B (49.5%) were observed, followed by group A (27.0%), O (13.5%) and AB (8.1%) (Guleria et al, 2005). Our population has shown possible association of blood group AB^{+ve} with gallbladder cancer (Singh et al, 2012). A New Delhi based study showed the GBC patients ratio of men and women to be 0.36: 1.00 (Batra et al, 2005).

The incidence rate ranges from 10 per lakh in Delhi to 2-3 per lakh in South India (Pandey et al, 2008). Within the Indian population, it is much higher in the northern cities, e.g, incidence in Delhi is 3.7 per lakh for males and 8.9 per lakh for females and in Bhopal it is 1.6 and 2.5 per lakh for males and females, respectively. In southern cities, e.g, in Chennai incidence is 0.5 per lakh for males and 0.8 per lakh for females and in Bangalore incidence for males is 0.6 per lakh and for females it is 0.7 per lakh population (Indian Council of Medical Research, ICMR; 2001). Gallbladder cancer cases in females rank 3rd in Guwahati, 4th in Chandigarh, Gwalior and 5th in Mumbai and Dibrugarh (National Cancer Registry Program, HBCR Report 2007-2011; Barbhuiya et al, 2009). This peculiarity of variations in occurrence of GBC between North and South (in India) makes one suspect that variation in dietary habits could be an important factor related to the etiology of GBC. Malhotra et al, (1968) has reported the variations of dietary habit in Northern and Southern parts of India. Age adjusted incidence rates of GBC among women are 10.2 per lakh in Kamrup urban district, 8.4 per lakh in Delhi, 7.1 per lakh in Aizawl district, 5.8 per lakh in Dibrugarh district, 5.6 per lakh in Imphal west, 5.1 per lakh in Silchar town,

4.4 per lakh in Bhopal, 2.1 per lakh in Mumbai, 0.9 per lakh in Bangalore, 0.9 per lakh in Chennai and 0.5 per lakh in Barshi (PBCR 2003-04) (Figure 1). Its incidence has been increasing in the Ganges delta (Kaushik et al, 1997), reason of which is still not clear. The incidence of gallbladder cancer parallels the prevalence of GSD; large and longstanding gallstones being associated with a higher risk of GBC (Kapoor et al, 2003).

Current Trend of GBC in Central India: Our Experience at Cancer Hospital and Research Institute, CHRI, Gwalior (2004-13): We have conducted an epidemiological survey at CHRI during 2004-2013. Out of 2614 total billary tract cancer cases registered at CHRI, Gwalior, about 2000 cases were gallbladder cancer. Generally, gallbladder cases were referred to the cancer hospital on the basis of general clinical symptoms and USG imaging from various hospitals. However, further CT and cytological investigations confirmed 2000 gallbladder masses with or without stones to be tumors. Gallbladder stones were found in more than 80% of the gallbladder malignancies. The highest number of GBC cases was recorded in the year 2010 followed by the year 2012 (Figure 2). Maximum number of GBC and GSD patients were registered from Gwalior (223 & 137) followed by Jhansi (137 & 64) and Morena (111& 54), respectively (Figure 3 & 4). Female to male ratio of GBC is 2 (Figure 5, 6 & 7). Gallbladder cancer was the 4th most common cancer at CHRI, Gwalior, during the 10 year tenure (Figure 8). Many (40%) of the GBC patients recorded a low BMI. Farmers (44.17%), followed by labourers (17.61%) constituted the major chunk of GBC patients. Majority of cancer cases were registered to be non-alcoholic (78.9%) and non-smokers (48.71%). Source of drinking water of most of the patients was bore-well (53.73%), followed by public water supply (38.8%). The source of water may also be one of the major reasons for gallstone formation and gallbladder cancer in the north central India region. The low-income group of people (below Rs. 70,000/- annual income) constituted the highest number of GBC patients. The lower caste Hindu (Vaishya and Sudra) people were mostly found to be affected, with lower caste people constituting the highest percentage amongst males. The highest percentage (78%) of people with GBC was vegetarian.

Our ten year epidemiological investigation (2004-13) showed high incidence of GBC in north central India, and identified females in the age group 41-50 to be at higher risk of GBC (Barbhuiya *et al*, 2009; in press 2015; Singh, 2015-PhD thesis).

Future Perspectives and Messages

The current increasing trend of gallbladder cancer cases in India, especially north central India, has greatly impacted the patients and clinicians. Development of potential biomarker for early diagnosis is still a challenge to all the investigators in the area. Our group in collaboration with other Institute are now focusing on to develop early biomarker from serum, tissue, bile, etc. We have identifed very potential molecules from tissue proteomic (Barbhuiya et al, 2011; Sahasrabuddhe et al, 2014) and methylome study. Presently, the living habits are aggreably considered to be the second most important causing factor after genetics make-up (predisposition) of gallbladder cancer individual. Since the availabile reports of ethnically varied incidence of gallbladder suggest association to the geographical location or belts, identification of the strata, though not known for their importance, where they belong to, are born and grown, need more priority to ascertain the future challenge to tackle the next carcinogenesis step. General conceptualization about "the association of gallstone with gallbladder cancer" among the common people is the need of hour. So, people who develop and complain of such diagnosis of stone formation need to decide whether they must remove gallbladder or not. Another interesting procedure which is required is about the precautions concerning diet. We need to know about their diet habits which results in the consequent biochemical and molecular changes of bile juice leading to saturation of bile, i.e., one of the mechanism of stone formation. Preliminary message is that precautions must be taken not to intake diets which influence and are associatd with stone formation, especially the families or populations who have family history of GBC and are supposed to be at risk of this cancer. The maiden diagnosis of gallstone indicates the possible development of future gallbladder cancer. So, it is suggested to consult the expert clinician as early as possible for an early and best treatement.

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IN FOCUS

MALIGNANT JAUNDICE: BRACHY THERAPY AS A TOOL

Introduction

Malignant obstruction of biliary tree can be caused by primary cholangiocarcinomas, local obstruction because of tumors of gallbladder or pancreas, or from metastatic disease to nodes at porta hepatis (1). At the time of diagnosis, only10- 20% of such patients are suitable for radical surgical resection and have a median survival time approaching 12-20 months. Approximately 65-70% of malignant biliary obstruction patients with unresectable disease are severely disabled because of jaundice, intense pruritus, loss of appetite, loss of weight, acholic stools, painful hepatomegaly, change in bowel habits, nausea, vomiting, and coagulopathies. Such patients have a median survival time of 2.7 months if no further therapy is given (2, 3). In this setting, given a short life expectancy, the therapeutic goal is often palliation of symptoms with major emphasis on quality of life (QOL). This is possible by drainage of the biliary system surgically, radiologically, or endoscopically.

There are two described methods to initially tackle the obstructive component before brachytherapy: -

1. By Percutaneoustranshepatic Biliary Drainage and Intraluminal Brachytherapy.
2. Endoscopic Metal Stent and Intraluminal Brachytherapy.

Technically, endoscopic decompression of the biliary tree is easier to perform than percutaneous drainage, but the percutaneous access to the biliary tree radiologically (ultrasound or fluoroscopic guided) is preferred over the endoscopic implantation in obstruction localized to the liver hilum or intrahepatic obstruction with little attendant morbidity (3). Percutaneous transhepatic biliary drainage (PTBD) alone, either externally or by the placement of an endoprosthesis to allow internal drainage, is able to palliate many patients with malignant biliary obstruction, but the effects are often limited with a median survival time of 6 months as these procedures do not provide effective treatment for underlying malignancy. Radiotherapy and chemotherapy have been tried for tumor mass reduction, but bile duct patency cannot be achieved with these methods alone. Hence, the idea of combination therapy using drainage procedures and radiotherapy has come up (4). Various studies have shown that after combining intraluminal brachytherapy (ILBT) with PTBD, median survival time improved when compared to that with the drainage procedures alone. Also, ILBT is easier to perform through PTBD, and treatment can be safely adapted for lesions in right and left hepatic as well as common bile ducts. The primary objective of brachytherapy is to reduce tumor stenosis and retard or avoid a renewed obstruction of the catheter by tumor ingrowth (3).

Review of Literature

Percutaneoustranshepatic Biliary Drainage and Intraluminal Brachytherapy: The management of malignant biliary obstruction remains a taxing problem for the physicians in all oncologic disciplines. The treatment of choice in these patients is radical surgery, but a complete resection is possible only in around one-fifth of patients. Even in these patients, negative margins are rarely achieved, and the rate of locoregional recurrences is between 25% and 64%. Also, morbidity and mortality of surgery are high, and the best achieved survival rates are below 10% at 5 years (1,8,9). In remaining patients, focus of current therapies remains palliation, and the objective is relief of obstructive jaundice by biliary bypass procedures. Without any therapeutic intervention, death results from recurrent cholangitis, sepsis, and hepatic failure secondary to biliary obstruction. Biliary decompression can be achieved through either surgical bypass or interventional radiologic procedures. Surgical palliative bypass has no advantage over radiologic or endoscopic method as palliative surgery has a high postoperative mortality up to 35% and morbidity up to 43% with survival time of 6-7 months (3, 10, 11). In view of risk of infecting the biliary tree and other complications including renal failure associated with surgical exploration in deeply jaundiced patients, biliary decompression is preferred by either percutaneous or endoscopic procedures, which may prevent the need for surgery.

Also, with these alternative procedures, a comparable median survival duration of 6-7 months is achieved (3). With the biliary drainage procedures, bile duct patency can be achieved but cannot be maintained because of local growth and spread of the tumor. Therefore, other treatment modalities, such as radiotherapy and chemotherapy have been tried to reduce the tumor mass.

Various studies in the 1990s using external beam radiotherapy (EBRT) in combination with biliary drainage procedures showed good symptom control and improvement in survival (5,7). Most of these lesions are adenocarcinomas, which are only moderately sensitive to radiation and therefore require high doses of radiation. However, this is not possible because of the critical structures, such as liver, duodenum, and stomach, which come into the radiation field, and therefore, only low doses of 40-50 Gy in 4-6 weeks can be delivered by EBRT because of poor tolerance of these organs (12). Encouraging results have been obtained by combining PTBD with ILBT that delivers a high dose of radiation in a short time to the central part of the tumor, which helps in maintaining the patency of ducts for a longer time and delaying in growth of the tumor, thus decreasing fatal complications because of biliary obstruction. Several techniques of ILBT have been described using 192 Ir source either at conventional low dose rate (LDR) or HDR. It has been reported that there is no difference in survival or complications between LDR or HDR brachytherapy after biliary drainage (13). However, HDR has its own advantages. There is no exposure to staff, treatment time is short in these otherwise sick patients, and prolonged interference with biliary drainage is avoided. Also, optimization is possible, radiation dose can be delivered to the desired tumor-bearing areas sparing the surrounding normal tissues, and treatment is completed in a few days, which does not require a prolonged hospital stay.

Many authors have reported a decrease in bilirubin levels as an indicator of palliation after treatment. Because these patients generally have a poor overall prognosis, durable symptomatic relief is an important end point, particularly from jaundice and its associated symptoms. Mornex et al (12) treated 7 patients with ILBT (192Ir wire) through either a percutaneous transhepatic catheter or surgically implanted external diversion catheter delivering a dose of 10-30 Gy (LDR) at 1 cm from the wire. All patients tolerated the procedure well and experienced symptomatic palliation. Mayer et al (14) treated 14 patients with unresectable bile duct tumors causing malignant obstructive jaundice with PTBD followed by HDR brachytherapy using 192Ir source delivering a total dose of 10 Gy (2.5 Gy per fraction, two fractions per day at 6-h interval for 2 days). Five patients also received EBRT. Palliation of jaundice and pruritus was seen in all 14 patients. In a study by Montemaggi et al (15), it was reported that jaundice was completely controlled in all 29 patients treated with biliary drainage and ILBT with or without EBRT and chemotherapy, and pain relief was seen in 11 (85%) of 13 patients.

In our centre also, we evaluated the role of HDR-ILBT through PTBD in the palliative management of malignant biliary obstruction and assess its role in symptom control and improvement in overall survival and QOL in these patients. In our study, 18 patients were recruited, and drainage by PTBD and subsequent treatment by ILBT were successfully performed in all the patients. We used the percutaneous access to the biliary tree because endoscopic placement of a drainage catheter into the stenosis localized in the liver hilum or intrahepatically is complicated and often unsuccessful. Moreover, intraluminal irradiation is easier to perform through a percutaneous catheter (3). The median survival duration in our patients was 8.27 months, and actuarial 6-month survival was 61.11%. Survival of patients in our study is comparable with that of patients in other reports of radiotherapeutic treatment of bile duct carcinomas (16). In 1981, Fletcher et al (18) reported treatment of patients with bile duct carcinoma with an internal 192Ir application. They found the median survival duration to be 11 months. Bruha et al (3) included 14 studies in a comparative analysis of patients with extrahepatic tumors of biliary tree treated with metallic stent implantation and radiotherapy. They observed that the mean survival time of such patients ranged from 4.6 to 14 months. Combination with intraluminal and/or EBRT could prolong it to 10-23 months (494 patients in 14 studies), thus approaching the survival after radical resection of extrahepatic bile duct carcinoma (up to 23 months). Pre- or postirradiation stenting was essential for such prolongation. Mayer et al (14) also reported the actuarial 2-year survival of 11.9% and a median survival of 6.5 months in all patients. The improved median survival duration indicates that patients treated with this technique achieve benefit, and this seems to compare favorably with the small group of patients, in whom radical surgery is performed. Also, median survival of our patient group was better than the survival figures after biliary drainage procedures alone (6-7 months) (3,19,21).

In a study by Thornton et al (19), the mean patency of biliary stents placed for malignant biliary obstruction was described to be approximately 8.5 months. The median overall survival time of 71 patients, who underwent primary stenting, was less than 6 months. Sut et al (20)

also reported the results of percutaneous transhepatic cholangiography and metal stenting for malignant biliary obstruction and concluded that the prognosis of these patients was extremely poor with none of the patient surviving for more than 193 days. Brountzos et al (21) analyzed 76 patients with malignant biliary obstruction who were treated with percutaneous placement of metallic stents and found a mean overall primary stent patency of 120 days and mean overall survival time of 142.3 days. Qian et al (22), in their analysis of 49 patients of malignant biliary obstruction treated with PTBD followed by local treatment, also concluded that local tumor therapy could prolong the survival time of such patients and may improve stent patency. In our setup, where most patients cannot afford costly stents and do not tolerate its attendant complications, we have used the described technique of PTBD followed by ILBT with equivalent results and minor complications only. ILBT retards or avoids the renewed obstruction of the catheter by tumor ingrowth, thus prolonging the symptom-free interval and survival in many patients. Thus, with this treatment approach, survival may be increased despite the lack of regional or distant control.

Cholangitis is the most frequent complication of ILBT, occurring in 44% of patients (16). Bruha et al (3) reported that 44% of patients treated with ILBT and metallic stenting developed cholangitis and commented that there were no complications directly because of brachytherapy. Gonzalez et al (23) reported a 30% cholangitis rate in patients treated with EBRT with/without ILBT, and this high rate may possibly be related to poor patient performance status. Apart from cholangitis, hemobilia, duodenal ulceration, and intrahepatic abscess have also been reported in the setting of these malignancies that are treated by either ILBT alone or other nonradiotherapeutic modalities (13,15, 24, 25). The rate of gastroduodenal ulceration and bleeding has been reported to be as high as 31% in a series using metallic stent and ILBT with/without EBRT (26). Furthermore, in studies using ILBT without metallic stent, complications of gastrointestinal bleeding and/or ulcer were rarely observed (14, 24, 25). There is no conclusive data regarding the optimum number and size of fractionation and total radiation dose in ILBT for achieving best palliation and minimizing complications.

Total dose varies by series, depending partly on the use of EBRT and on whether LDR or HDR techniques are used, making it difficult to compare series (27, 28). In a study by Kim et al (28), no serious treatment related complications were noticed in their patients who were treated with a total ILBT dose of 15 Gy in three fractions (HDR). However, the HDR brachytherapy working group has proposed a dose of 30 Gy (6 _ 5 Gy) specified at 1 cm from the radiation source for palliative ILBT in patients of extrahepatic bile duct cancers (29). In our centre, a total HDR-ILBT dose of 16 Gy (8 Gy per fraction in two fractions 1 week apart) produced no serious complications with durable symptom control and comparable overall survival compared with other brachytherapy dose schedules and even without the use of EBRT. Clogging of the biliary catheter can be a problem during the follow up of these patients which can be restored either by exchanging bile drains or flushing the catheter. We have not encountered any cases of bile duct fibrosis as reported by Kopelson et al (30).

Endoscopic Metal Stent and Intraluminal Brachytherapy: Self-expandable metal stents (SEMS) are excellent modality for palliation of hilar block. SEMS are placed by either percutaneous or endoscopic routes. Endoscopic stent placement is technically more difficult but is associated with lower rates of complications. Endoscopic drainage is the treatment of choice for malignant hilar biliary obstruction. Bilateral stenting is difficult and is attended with high rate of complications. Dowsett et al (47) showed that drainage of 25% of liver volume is usually enough for palliation of symptoms and leads to improvement in clinical, biochemical and radiological parameters. Unilateral endoscopic drainage is effective in these patients (31, 32). We have shown in our previous study (33) that the problem of cholangitis can be tackled by using contrast-free technique of stenting, but stent occlusion by tumor ingrowth or overgrowth continues to be an important limitation (48).

Radiation therapy with stenting has shown encouraging results (34-42,44-46). Addition of ILBT by using Ir-192 to metallic stenting is effective in preventing tumor ingrowth and prolongs biliary patency (37,43,46). Iridium-192 is a gamma emitter and allows delivery of high-dosage radiation to a well-defined and limited volume of tissue. ILBT is particularly suitable for malignant tumors of bile duct because they are usually localized and external beam radiotherapy use is limited by the poor tolerance of surrounding organs (49). There are a number of studies which have used metallic stents with ILBT with

or without external beam radiotherapy for palliation of malignant biliary obstruction. Kocal et al (44) in their analysis of eight recent studies found that the mean stent patency and survival reported in these studies was 7.5 and 11.2 months, respectively.Bowling et al (50) in a retrospective study compared percutaneous transhepatic stenting alone versus stenting plus radiotherapy (external beam radiotherapy and brachytherapy).Median survival was 7 months in stent alone group and 10 months in stenting with radiotherapy group (50). Bruha et al. (37) used combination of intraluminal brachytherapy and metallic stents by percutaneous route in 11 patients with hilar block owing to nonresectable gallbladder carcinoma. The mean duration of stent patency was 220 days and the mean survival was 237 days (37). Reported survival has ranged from 3 weeks to 3 years (51) following ILBT.

In the series of 19 patients, [Fletcher and associates (35)], median survival was 11 months and 1 year survival was 47%. There are no studies in literature comparing contrast-free metal stenting plus ILBT with contrast-free metal stenting alone. We did contrast-free metal stenting with ILBT in eight patients with hilar block owing to carcinoma gallbladder and 10 patients of contrast-free stenting acted as historical controls. We compared the mean survival and mean duration of stent patency in patients with stent plus ILBT with stent alone group and found it to be significantly higher. Hemobilia, cholangitis, and intrahepatic abscess have been described in literature as potential complications of brachytherapy. Duodenal ulcers have been reported in as high as 31% in patients treated with metallic stents plus ILBT (46). In our study, 2/8 (25%) of patients developed duodenal ulcers which responded to therapy with proton pump inhibitors. In conclusion, contrast-free unilateral metal stenting with ILBT is a safe and effective method of palliation for malignant hilar biliary obstruction and appears to prolong stent patency and patient survival.

Conclusions

Both PTBD followed by ILBT and endoscopic SEMS with ILBT are feasible procedures to achieve good symptom control, minimal complications, and improvement in survival and QOL. Biliary decompression can alleviate anorexia, forestall sepsis, and hepatic failure; and intrabiliary irradiation may help in delaying restenosis.

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